UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,046	10/01/2001	Liang Xu	2444-105-1	8537

6449 7590 07/28/2005

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,046	XU ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,12,26-28,30-35,38-45,47-50,53-59,61 and 63-74* is/are pending in the application.

4a) Of the above claim(s) *26-28,30-35,38-45,47-50,53-59,61,63-68 and 70-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,12,69,73 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and the Declaration of Esther Chang, both filed 5/31/05, are acknowledged and have been entered.

2. Applicant is reminded of Applicant's election with traverse of Group II (claims 1-4, 7, 8, 12, 69 and newly added claims 73 and 74), and species of immunoliposome comprising a pre-linked antibody fragment that binds a transferrin receptor and further comprises DNA encoding wild type p53 in Applicant's said responses filed 8/27/04 and 4/30/04. Upon further consideration, Group I has been rejoined to Group II.

Claims 26-35, 38-50, 53-61, 63-68 and newly added claims 70-72 (non-elected groups III-X) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-4, 7, 8, 12, 69, 73 and 74 are currently being examined.

3. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 7, 8, 12 and 69 is deemed to be the filing date of PCT US00/04392, i.e. 2/22/00, as the parent provisional application 60/121,133 does not support the claimed limitations of the instant application. The limitations of the ratios recited at the last 3 lines of claim 1, "MPB" in claim 8.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 7 and 8 are indefinite in the recitation of "immunoliposome complex of claim 6" because claim 6 is a canceled claim.

b. Claim 8 recites "said antibody or" at line 2. There is insufficient antecedent basis for this limitation. It is noted that claim 8 depends upon canceled claim 6, which depended upon base claim 1. The limitation "antibody" has been deleted from claim 1 by Applicant in the amendment filed 5/31/05.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3, 7, 12, 73 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al (Oncogene 11: 1383-1388, 1995) in view of Wang et al (Bioconjugate Chemistry 8: 878-884, 1997), Nilsson et al (Current Opinion in Structural Biology 2: 569-575, 1992) and Martin et al (J. Biol. Chem. 257(1): 286-288, 1982, previously provided).

Yu et al teach cationic liposome-mediated E1A gene transfer (DNA) significantly inhibited growth and dissemination of ovarian cancer cells that overexpress HER-2/neu in treated mice. Yu et al further teach using a DNA: liposome ratio of 1:13, a ratio that is within the range that is recited in instant claim 1. Yu et al teach that the liposomes can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor (especially abstract, page 1385 at column 1 at the first full paragraph, page 1387 at column 1 at the first full paragraph).

Yu et al do not teach the method nor ratio of incorporation of antibody that is an scFV into liposomes by direct conjugation via a sulfur atom that was a part of a sulfhydral group at a carboxy terminus on the scFv.

Wang et al teach generating an scFv with anti-CD19 specificity with a carboxy terminal cysteine, i.e., contains a sulfhydral group, for the purpose of covalently linking the scFv-cys with a toxin through a disulfide bond, and using the scFv linked to the toxin to effectively target the toxin to CD19-expressing B cell lymphomas and leukemias and that the disulfide bond did not interfere with the antigen binding activity of scFv. Wang et al teach that advantages of using scFv rather than intact antibody is smaller size for better tumor tissue penetration (especially abstract, page 1 at the first two paragraphs, paragraph spanning pages 882 and 883, and first sentence of the last paragraph on page 883).

Nilsson et al further teach targeting drugs to a specific cell type using monoclonal antibodies. Nilsson et al teach that scFv fragments have simplified the production of recombinant antibody fragments in bacteria and have the same affinity as the corresponding full-length antibody (especially paragraph spanning pages 572-573).

Martin et al teach irreversible coupling of immunoglobulin Fab' fragments to liposomes at ratios of upwards of/including 250 ug of Fab' fragments to 1-2 umol of vesicle phospholipids (w:w ratio of about 1:24-1:48) or 1.4 umol/ml lipid (in liposomes) to Fab' at 0.5-4.0 mg/ml (w:w ratio of about 1:14 protein to lipid to about 1:2 protein to lipid) using direct coupling via a sulfur atom on the Fab' and using MPB. Martin et al further teach that their method provides improved coupling efficiencies and leads to the formation of a stable antibody-vesicle linkage. Martin et al teach that it should be possible to link any thiol-containing protein ligand to MPB-PE containing liposomes, that coupling via the thiol group on the Fab' fragment results in favorable orientation on the vesicle surface and reduces the possibility of vesicle aggregation. Martin et al teach the absence of the Fc region of the antibody is desirable to eliminate the possibility of Fc-mediated binding and complement activation. Martin et al also teach cytoplasmic delivery of liposomal contents (see entire article, for example, abstract, page 286 at column 2 at the third full paragraph, Results, and Discussion).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an scFv antibody such as taught by Nilsson et al with a carboxy terminal cysteine residue such as the scFv-cys antibody fragment taught by Wang et al having the anti-P185 antibody specificity taught by Yu et al, and to have coupled it to the cationic immunoliposome comprising the E1A encoding DNA taught by Yu et al using the method taught by Martin et al, i.e., coupling directly to the liposome via use of MPB to utilize conjugation through the sulfur atom on the scFv-cys.

One of ordinary skill in the art would have been motivated to do this in order to target the immunoliposome containing E1A DNA taught by Yu et al to p185-expressing HER-2/neu tumors with improved efficacy because: (1) Yu et al teach targeting of their said immunoliposomes using an antibody with anti-p185 specificity to improve on the inhibition of growth and dissemination of ovarian cancer cells obtained using their untargeted liposome, (2) Martin et al teach irreversible and stable coupling of antibody fragments to liposomes, including liposomes intended for cytoplasmic delivery of liposomal contents, using a method that provides improved coupling efficiencies and that can be used to link any thiol-containing protein ligand to MPB-PE containing liposomes in a favorable orientation, and that using an antibody fragment that does not possess the Fc region of the antibody is desirable to eliminate the possibility of Fc-mediated binding and complement activation, (3) Nilsson et al teach the advantage of using scFv is to simplify the production of recombinant antibody fragments in bacteria and that the scFv have the same affinity as the full length antibody, and (4) Wang et al teach scFv-cys with specificity to another tumor antigen that can be used target a toxin conjugated via the cysteine to a tumor expressing the tumor antigen, and that the smaller size of the scFv-cys is advantageous in comparison with intact antibody because it is smaller and would be better suited for tumor tissue penetration than the intact antibody. In addition,

the scFv-cys lacks the Fc region of the antibody, and Martin et al teach that it is advantageous to use fragments lacking the Fc region to avoid complement activation.

Applicant's arguments to Martin et al in Applicant's amendment filed 5/31/05 have been fully considered, but are not persuasive.

Applicant's arguments to Martin et al are of record in the said amendment in the paragraph spanning pages 20-21, briefly that the ratio claimed in the instant claims is 0.025 mg/1.4 umol to 0.2 mg/1.4 umol which is outside the ratio taught by Martin et al.

It is the Examiner's position that the instant claims do not recite a weight to umol ratio for protein to lipid, but rather recite a weight to weight ratio, nor do the instant claims recite the lipid used, and the weight to weight ratios taught by Martin et al fall within the range recited in the instant claims as enunciated in the instant rejection.

8. Claims 1-4, 7, 8, 12, 69, 73 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2004/0209366 A1 in view of Wang et al (Bioconjugate Chemistry 8: 878-884, 1997), Martin et al (J. Biol. Chem. 257(1): 286-288, 1982, previously provided), Xu et al (Human Gene Therapy: 467-475, 1997, IDS reference) and U.S. Patent No. 6,200,956 B1.

US 2004/0209366 A1 discloses use of a targeting moiety such antibody fragments such as scFv or Fab' linked to an effector cationic lipid nucleic acid complex, i.e., an immunoliposome loaded with an effector molecule, provides the ability to conveniently customize the complex for delivery to specific cells and tissues. US 2004/0209366 A1 discloses that the antibody may be attached to the liposome either before or after the formation of the nucleic acid:lipid complex. US 2004/0209366 A1 further discloses that an example of an effector is a nucleic acid molecule encoding a tumor suppressor gene such as p53 that can be specifically targeted to cells such as cancer cells using a targeting moiety. US 2004/0209366 A1 discloses that for *in vivo* applications, cholesterol is used as a helper lipid, whereas for *in vitro* applications, DOPE is used as a helper lipid. US 2004/0209366 A1 discloses that the ratio of DNA to lipid is 1 ug/8-12 nmol, and the ratio of antibody to lipid is 15.6 ug of scFv to 1 umol lipid, or on a w:w basis 1: 12.2 which is in the range recited in instant claim 1. US 2004/0209366 A1 discloses that immunoliposomes of the invention were capable of delivery of liposome-encapsulated anti-cancer drug to target cells (see especially [0019], [0036], [0137], [0150], [0165], Examples 5 and 7).

US 2004/0209366 A1 does not disclose wherein the scFv is covalently bound to DOPE linked to MPB, nor wherein the scFv is capable of binding to a transferrin receptor and the nucleic acid encodes a wild type p53.

Wang et al teach generating an scFv with anti-CD19 specificity with a carboxy terminal cysteine, i.e., contains a sulfhydral group, for the purpose of covalently linking the scFv-cys with a toxin through a disulfide bond, and using the scFv linked to the toxin to effectively target the toxin to CD19-expressing B cell lymphomas and leukemias and that the disulfide bond did not interfere with the antigen binding activity of scFv. Wang et al teach that advantages of using scFv rather than intact antibody is smaller size for better tumor tissue penetration (especially abstract, page 1 at the first two paragraphs, paragraph spanning pages 882 and 883, and first sentence of the last paragraph on page 883).

Martin et al teach irreversible coupling of immunoglobulin Fab' fragments to liposomes at ratios of upwards of/including 250 ug of Fab' fragments to 1-2 umol of vesicle phospholipids (w:w ratio of about 1:24-1:48) or 1.4 umol/ml lipid to Fab' at 0.5-4.0 mg/ml (w:w ratio of about 1:14 protein to lipid to about 1:2 protein to lipid) using direct coupling via a sulfur atom on the Fab' and using MPB. Martin et al further teach that their method provides improved coupling efficiencies and leads to the formation of a stable antibody-vesicle linkage. Martin et al teach that it should be possible to link any thiol-containing protein ligand to MPB-PE containing liposomes, that coupling via the thiol group on the Fab' fragment results in favorable orientation on the vesicle surface. Martin et al teach the absence of the Fc region of the antibody is desirable to eliminate the possibility of Fc-mediated binding and complement activation. Martin et al also teach cytoplasmic delivery of liposomal contents (see entire article, for example, abstract, page 286 at column 2 at the third full paragraph, Results, and Discussion).

Xu et al teach transferrin-cationic liposomes mixed with DNA encoding wild type p53. Xu et al teach use of the nucleic acid transferrin-cationic liposomes are effective for transfection of tumor cells, administration results in significant inhibition of tumor growth and prevents relapse and metastasis of mammary tumors in nude mice, and for treatment of head and neck cancer.

U.S. Patent No. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell, i.e., is an immunoliposome, and further comprising DNA that is to be delivered to the said target cell type, i.e., is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. Patent No. 6,200,956 B1 further discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin receptor, i.e., are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted immunoliposome such that as used for delivery of an effector DNA to breast cancer cells disclosed by US 2004/0209366 A1, but that would instead be useful in delivering the (wild type) p53 effector to other types of tumor cells for treatment of head and neck cancer as taught by Xu et al as in their immunoliposome, by using a smaller molecule than transferrin such as the scFv antibody fragment in place of transferrin as a targeting moiety, said scFv such as disclosed by US 2004/0209366 A1 where the scFv was to be coupled indirectly to the liposome or an scFv-cys as taught by Martin et al where the scFv-cys was to be conjugated directly to the immunoliposome using MBP as taught by Martin et al, said scFv or scFv-cys having specificity for the transferrin receptor like the antibodies with anti-transferrin receptor specificity disclosed by U.S. Patent No. 6,200,956 B1, and to have used cholesterol as the helper lipid when the application was intended for *in vivo* use and DOPE as the helper lipid when the application was intended for *in vitro* studies as disclosed by US 2004/0209366 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer of the head and neck more effectively because: (1) U.S. Patent No. 6,200,956 B1 discloses using scFv or Fab' antibody fragments linked to effector cationic lipid nucleic acid complexes provides the ability to conveniently customize the complex for delivery to specific cells and tissues such as to tumor cells, and teaches helper lipids to be used in the targeted immunoliposome carriers, (2) Xu et al teach using a transferrin-targeted immunoliposome with the effector molecule wild-type p53 is useful for treatment of head and neck cancer, (3) Wang et al teach that it is advantageous to use scFv rather than intact antibody because the smaller size is better for tumor tissue penetration and that an scFv-cys specific for a tumor cell antigen could be used linked to a toxin for tumor targeting through the sulfur atom on the cys without loss of antigen binding activity to the B cell lymphomas and leukemias, (4) Martin et al teach that it is advantageous to use antibody fragments that do not contain the Fc region, i.e., such as Fab' (or scFv) in order to eliminate the possibility of complement activation, (5) U.S. Patent No. 6,200,956 B1 discloses that transferrin and anti-transferrin receptor antibodies or antigen binding fragments thereof are ligands of the target cell surface transferrin receptor, (6) US 2004/0209366 A1 discloses that nucleic acid encoding p53 is an effector for cancer cells, (7) Martin et al teach irreversible and superior coupling efficiency of Fab' fragments to liposomes via direct conjugation via a sulfur atom on the Fab' using MPB, and that it should be possible to link any thiol-containing protein ligand to MPB-PE containing liposomes including because the coupling via the thiol group results in favorable orientation on the vesicle surface, (7) U.S. Patent No. 6,200,956 B1 discloses and Martin et al teach using antibody fragments such as scFv or Fab' at w:w ratios to lipid recited in instant claim 1 and U.S. Patent No. 6,200,956 B1 discloses DNA(nmol) to lipid (ug) ratios recited in

instant claim 1, and (8) the transferrin molecule taught by Xu et al is almost three times as large as the scFv-cys or scFv fragments disclosed/taught by U.S. Patent No. 6,200,956 B1 and Wang et al, and the said fragments have the art taught advantage of being more effective for penetrating tumor tissue.

Applicant's arguments to Martin et al in Applicant's amendment filed 5/31/05 have been fully considered, but are not persuasive.

Applicant's arguments to Martin et al are of record in the said amendment in the paragraph spanning pages 20-21, briefly that the ratio claimed in the instant claims is 0.025 mg/1.4 umol to 0.2 mg/1.4 umol which is outside the ratio taught by Martin et al. Applicant's arguments to Xu et al are of record in the said amendment on pages 29-30, namely that transferrin at 80 kDa is larger than scFv at 28 kDa, that transferrin binds to the liposome through simple mixing, that the amount of transferrin used by Xu et al is different than that recited in instant claim 1 for scFv.

It is the Examiner's position that the instant claims do not recite a weight to umol ratio for protein to lipid, but rather recite a weight to weight ratio, nor do the instant claims recite the lipid used, and the weight to weight ratios taught by Martin et al fall within the range recited in the instant claims as enunciated in the instant rejection. It is the Examiner's position that the fact that transferrin is much larger than scFv provides motivation to combine the references in the instant rejection and that although Xu et al teach using an amount of transferrin different from that recited in instant claim 1, it would have been prima facie obvious to have used the amount of protein taught by Martin et al because the scFv or scFv-cys antibody fragment was the protein being coupled, and that amount is the same as recited in instant claim 1.

9. No claim is allowed.

10. It is noted by the Examiner that the Duncan et al reference discussed by Applicant in the amendment filed 5/31/05 and in the Declaration of Dr. Chang at paragraphs # 5-9 is not cited in the instant rejections and as it was not listed on a Form 1449 by Applicant, it has not been considered by the Examiner. Likewise, the Allen et al paper submitted with the said Declaration and not reference by Applicant was not listed on a Form 1449 by Applicant, and it has not been considered by the Examiner.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
July 15, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600